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REVIEW ARTICLE

Long-term management of thrombocytosis in essential thrombocythaemia

Gunnar Birgegård

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Abstract Essential thrombocythaemia (ET) is an acquired myeloproliferative disorder with a prolonged clinical course and a near-normal life expectancy. Therapy is stratified according to risk of thrombohaemorrhagic events. In high-risk patients, platelet reduction is generally recommended. In intermediate-risk patients, therapy should be considered depending on the severity of associated risk factors, especially cardiovascular. In low-risk patients, a watch-and-wait approach is appropriate. Hydroxycarbamide is generally first-line therapy. Concerns for possible leukemogenicity make anagrelide or interferon-α possible choices in younger patients and those who are resistant or intolerant to hydroxycarbamide. Each pharmacotherapy is associated with specific long-term risks and benefits. The potential risk of major bleeding is the main drawback of aspirin. Hydroxycarbamide is an established, effective drug for ET, but it may increase the risk of transformation to acute myeloid leukaemia and may give mucocutaneous ulcers. Anagrelide is a licensed treatment that also reduces platelet counts and is generally well tolerated, with evidence that some common side effects diminish over time. Anagrelide can have cardiac effects due to inhibition of phosphodiesterase III and therefore requires cautious use in patients with cardiac insufficiency. There is no evidence of leukaemogenicity with anagrelide or interferon-α therapy. Interferon-α is the only treatment suitable for use during pregnancy, although it is not licensed in ET. While it is effective for platelet reduction, the use of interferon-α is restricted by psychiatric side effects. Our knowledge of the optimum pharmacotherapy for each patient with ET continues to evolve through research and clinical trials, particularly into the molecular basis of the disease.

Keywords Essential thrombocythaemia · Anagrelide · Hydroxycarbamide · Interferon · Myeloproliferative disorder

Introduction

Essential thrombocythaemia (ET) is an acquired myeloproliferative disorder (MPD), characterised by persistent peripheral thrombocytosis and a tendency for thrombosis and haemorrhage [1]. For example, in a study of 93 patients with ET, at a median follow-up of 70 months, 16% of patients developed thrombosis, 14% developed haemorrhage and 17% developed microvascular complications [2]. ET can proceed in some cases to myelofibrosis, acute myeloid leukaemia (AML), myelodysplastic syndromes (MDS) or polycythaemia vera (PV) [3]. The estimated annual incidence of ET based on World Health Organization (WHO) criteria is 1–2.5/100,000 individuals [4]. However, the true incidence is likely to be higher as many patients are without symptoms, and thus undiagnosed. Even though ET is a rare disease, the prevalence is high at 30/100,000 general population [1], reflecting the near-normal life expectancy of patients with the condition [5].

Several lines of evidence suggest that ET is a heterogeneous disease entity, though the existence of distinct subgroups is difficult to validate. Molecular evidence includes the patient's JAK2 mutation status (i.e. the presence or absence of the Janus kinase 2 mutation *JAK2V617F*) [3], variation in X-chromosome inactivation

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G. Birgegård (✉)
Department of Haematology, Division of Medicine,
Institution for Medical Sciences, University Hospital,
Uppsala 75185, Sweden
e-mail: gunnar.birgegard@medsci.uu.se

patterns in females [6] and differences in PV rubra vera-1 (PRV1) mRNA expression (discriminating two types of ET) [7], while immunohistochemical evidence includes heterogeneous *c-mpl* expression [8]. Differences have also been observed between patients with ET in the growth of erythropoietin-independent colonies (EEC). In a study of molecular markers, growth of EEC was observed in 50–69% of ET patients [7, 9]. Furthermore, as a group, ET patients with the *JAK2V617F* mutation and/or low serum erythropoietin levels seem to have a more PV-like phenotype with slightly higher white blood cell counts and haemoglobin levels [3, 10, 11].

Diagnosis

The diagnosis of ET includes detection of specific changes in bone marrow morphology, as well as exclusion of secondary thrombocytosis caused by other conditions [12]. Recently, an advisory group to the WHO proposed revised diagnostic criteria for ET (Table 1) [12]. Using these criteria, diagnosis is supported by demonstration of a clonal marker of the condition (e.g. *JAK2V617F*, present in approximately 50% of ET patients) [3]; however, identification of this mutation cannot differentiate between ET and other MPDs. Several investigators suggest that some ET patients diagnosed according to the guidelines of the Polycythaemia Vera Study Group actually have an early stage chronic primary myelofibrosis (PMF-0 or 'false ET') [13, 14]. This prefibrotic condition is known to progress to overt myelofibrosis in a high proportion of patients, thus differing from 'true ET' which does not [15–17]. If this distinction is valid, it is an important consideration when evaluating treatment strategies. However, the feasibility of distinguishing ET from PMF-0 is not generally accepted among pathologists in clinical practice [18].

Table 1 New World Health Organization (WHO) proposed classification for essential thrombocythaemia [12]

All the following criteria must be met to diagnose essential thrombocythaemia:

- Sustained platelet count $\geq 450 \times 10^9$/l (reduced from $\geq 600 \times 10^9$/l)
- Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis
- Does not meet the WHO criteria for polycythaemia vera, primary myelofibrosis, chronic myelogenous leukaemia, myelodysplastic syndromes or other myeloid neoplasms
- Demonstration of *JAK2V617F* mutation or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis

The ideal therapeutic agent?

A number of pharmacotherapies have been investigated for use in ET. The ideal therapeutic treatment should rapidly lower platelet counts to normal levels, reduce ET-related complications and symptoms, have limited side effects and no long-term safety concerns. Long-term benefits and risks of pharmacotherapy are of particular relevance to patients with ET, who require prolonged treatment over a lifetime. This article considers the long-term effects of several ET treatment options, focusing on the anti-platelet agent, aspirin, and three cytoreductive therapies: hydroxycarbamide, anagrelide and interferon-α. Taking these findings into consideration, a risk-based treatment algorithm for ET is proposed.

Literature search

This article contains information from a number of sources, including relevant searches of PubMed (conducted on 14 November 2007), the author's own reference database and the reference lists of recent review articles. It is not intended as a systematic review.

Acetylsalicyclic acid (aspirin)

Since it was first synthesised in 1897, the use of aspirin has extended from analgesia to encompass prevention of cardiovascular events such as myocardial infarction and ischaemic stroke [19]. Theoretically, aspirin also has a place in the management of ET, particularly as it has been shown to suppress excess thromboxane synthesis [20], evident in patients with ET and PV [20, 21]. Several studies have confirmed this theory, showing that aspirin reduces thrombotic complications associated with ET [22, 23] as well as microvascular events (e.g. neurological symptoms and erythromelalgia) [24, 25].

The only randomised controlled trial investigating use of aspirin in this area was performed in patients with PV, a related MPD [26], which calls into question the direct applicability of the results. In the placebo-controlled European Collaboration on Low-dose Aspirin in PV (ECLAP) study, low-dose aspirin (100 mg/day) significantly reduced the risk of thrombotic complications (non-fatal myocardial infarction and stroke, death from cardiovascular causes, pulmonary embolism and major venous thrombosis) [26].

Any long-term therapeutic benefit of aspirin should be weighed against the potential risk of a major bleeding episode and gastrointestinal side effects. The relative risk of major bleeding with aspirin was 1.62 in the ECLAP study, which was consistent with results in non-PV patients [26].

Use of aspirin should therefore be avoided in patients with a history of bleeding or with very high platelet levels (greater than $1{,}500\times10^9$/l) because of an increased risk of haemorrhage [27]. Taking the observational and theoretical evidence into account, aspirin may have a role for the management of ET, particularly for patients at low risk of haemorrhagic complications. Noteworthy, however, is that health economic studies calculating the value of health gain versus the loss of health due to complications of aspirin therapy have not been undertaken in ET.

Hydroxycarbamide

Hydroxycarbamide, also known as hydroxyurea, is a non-specific, cytotoxic, myelosuppressive agent that is used to treat all MPDs, including ET. Its mechanism of action involves inhibition of ribonucleotide diphosphate reductase activity, thus blocking the cell cycle at the G_1/S phase and resulting in cell death [28].

Hydroxycarbamide is an established drug with proven platelet-reducing efficacy [29–33] and is generally well tolerated [31, 32]. Results from two randomised controlled trials confirm that hydroxycarbamide reduces the risk of thrombotic events in high-risk patients with ET [29, 30]. The Italian study by Cortelazzo et al., in which patients were randomised to receive hydroxycarbamide (n=56) or no myelosuppressive therapy (n=58), reported the number of thrombotic episodes to be significantly lower in the hydroxycarbamide group than in the control group (3.6% and 19.0%, respectively; p=0.003) [29]. Noteworthy is that about 70% of patients in both groups also received anti-platelet prophylaxis. The United Kingdom Medical Research Council Primary Thrombocythaemia 1 study (MRC PT-1) compared hydroxycarbamide plus aspirin (n=404) with anagrelide plus aspirin (n=405) [30]. Rates of major arterial and venous thrombosis in the hydroxycarbamide arm (4.2% and 3.5%, respectively) were similar to those observed in the hydroxycarbamide group of the Cortelazzo study [29, 30]. The incidence of venous thrombosis was significantly lower in the anagrelide arm than in the hydroxycarbamide arm (p=0.006), whereas the incidence of arterial thrombosis was lower in the hydroxycarbamide arm (p=0.004). However, the reasons behind these observations are unclear. Five patients developed myelofibrosis in the hydroxycarbamide group versus 16 in the anagrelide group; raising the possibility that hydroxycarbamide may give better protection against fibrosis. Significantly fewer haemorrhagic events occurred in the hydroxycarbamide group than in the anagrelide group, 8 versus 22, respectively (p<0.008). The latter finding may be due to a synergistic effect between anagrelide and aspirin when given concomitantly. No significant difference in the frequency of minor bleedings between treatment groups was observed [30]. It is noteworthy that a separate randomised controlled investigation (ANAHYDRET study) compared hydroxycarbamide and anagrelide in 258 previously untreated ET patients diagnosed according to the WHO criteria [34]. The 12-month findings, reported at the American Society of Hematology congress in 2007, showed no significant difference in the incidence of thromboembolic or haemorrhagic events (major events 8 versus 8 and minor events 22 versus 23 for thromboembolic and haemorrhagic events, respectively) between the hydroxycarbamide and anagrelide arms, suggesting non-inferiority for anagrelide. However, statistically low numbers preclude a firm conclusion at this timepoint [34].

There is strong evidence to suggest that concomitant or sequential use of hydroxycarbamide and an alkylating agent or radioactive phosphorous may increase the risk of malignant transformation in MPDs, possibly due to the radiosensitising effect of hydroxycarbamide [35–39]. This theory is supported by mechanism of action studies, which show that hydroxycarbamide prevents *de novo* DNA synthesis and repair [40]. Interestingly, the bone marrow of hydroxycarbamide-treated patients shows a dysplastic appearance, including left-shifting of myelopoiesis, macrocytosis of red cells and dysplasia of megakaryocytes, which is not seen with non-cytostatic drugs [41]. In clinical studies with more than 96 months median follow-up, transformation to AML/MDS occurred in 0–22% of patients with ET/PV treated with hydroxycarbamide as the sole therapeutic agent [33, 37, 42–46]. The only long-term study designed to investigate this endpoint shows that transformation to AML in hydroxycarbamide- or pipobroman-treated patients generally occurs after 10 or more years' therapy, with the incidence reaching 10–12% after 12 years [45]. In conclusion, the leukaemogenicity of hydroxycarbamide remains a concern that has not been diminished by recent data.

The most common side effects of hydroxycarbamide are granulocytopaenia and anaemia [47], especially after long-term treatment. Fever of unknown aetiology has also been observed following initiation of hydroxycarbamide therapy [48–50]. Cutaneous manifestations are commonly reported by patients receiving long-term hydroxycarbamide therapy and are the most frequent reason for treatment cessation [51–53]. Cutaneous complications include alopecia, xerosis and scaling, atrophy of the skin and subcutaneous tissues, skin and nail hyperpigmentation, and cutaneous and mucocutaneous ulceration [51, 52]. Furthermore, an association between long-term hydroxycarbamide therapy and multiple skin tumours, including squamous and basal cell carcinomas, has also been reported [54]. The lower-limb ulcers caused by hydroxycarbamide are often painful, and treatment must be withheld to allow the ulcers to heal, but

this occurs slowly and poorly, occasionally requiring grafting [55, 56]. In one study, 12 out of 133 patients (9.0%) receiving hydroxycarbamide developed leg ulcers, requiring a switch of treatment in ten of these patients [46]. Withdrawal rates of 8–20% due to adverse effects have been reported in trials [30–32, 46]. According to experts in the field [57, 58] and evidence-based guidelines [59], hydroxycarbamide is considered to be the first-choice cytoreductive therapy in high-risk patients with ET. However, approximately 15% of patients receiving hydroxycarbamide either do not achieve the desired reduction in platelet counts or develop unacceptable side effects [30–33, 46, 60]. In an attempt to standardise the definition of resistance and intolerance to hydroxycarbamide, thus when to stop treatment and switch to an alternative therapy, a working group consensus definition has recently been published (Table 2) [61].

Anagrelide

Anagrelide is a cytoreductive agent, with a selective effect on the megakaryocyte cell lineage [62]. It reduces platelet production by inhibiting megakaryocyte colony development, thus reducing megakaryocyte size, ploidy and maturation [63]. Several studies have shown that it effectively lowers platelet counts (overall response rate of 76–94%) and reduces ET-associated complications and symptoms [63–72]. Anagrelide has been shown in trials to be as effective as hydroxycarbamide, interferon-α and alkylating agents in reducing platelet counts, without the added complication of alkylating or cytotoxic properties [73], and can be used in patients who are intolerant or resistant to these cytoreductive agents [64].

Anagrelide is not mutagenic [74], and there is no known evidence to suggest that it is leukaemogenic [75]. In a long-term retrospective analysis, anagrelide did not result in excess conversion to AML, and no ET patient receiving anagrelide for more than 3 years transformed [64]. Moreover, in a study with a mean follow-up of 12.5 years, leukaemic transformation did not occur in any of the 39 ET patients treated with anagrelide [76].

Anagrelide is considered effective for reducing the incidence of thromboembolic and haemorrhagic complications. However, this effect has not been investigated in a placebo-controlled study. Supporting evidence rests mainly on the comparison with hydroxycarbamide; in particular, the study by Cortelazzo et al. [29] showing a reduction in thrombotic events with cytoreductive treatment, and the results of the PT-1 study [30], demonstrating a similar incidence of thrombotic events in the anagrelide and hydroxycarbamide arms to that reported in the Cortelazzo study. These two studies differed in terms of inclusion criteria and the use of aspirin; however, the incidence of thrombosis was the same in both hydroxycarbamide arms, indicating similarity of the population. The ANAHYDRET study demonstrated non-inferiority of anagrelide (for efficacy and ET-related complications) compared with hydroxycarbamide for the treatment of ET patients at 12 months follow-up ($p<0.025$) [34]. Furthermore, in a study of 79 patients with ET, anagrelide significantly reduced the rate of major thromboembolic complications compared with the pre-treatment period ($p=0.0455$) [65]. However, a clear clinical benefit in terms of haemorrhagic events has not yet been convincingly demonstrated.

The most common side effects of anagrelide include headache (13–35%) and tachycardia (9–21%), which arise due to the inhibitory properties of anagrelide on phosphodiesterase III [65, 66, 69, 70, 73, 77]. The majority of common side effects are mild or moderate (e.g. WHO grade 1 or 2) and manageable [63–66, 70, 72, 77], with the frequency and severity dose-dependent [63]. The incidence of serious side effects is higher in patients aged 60 years or older than in patients younger than 60 years [64]. Aggravation of cardiac insufficiency is a rare but important side effect, and special caution is advised in patients with previous cardiac failure [76, 78]. Anagrelide lowers red blood cell count by approximately 10% in about 30% of patients [63, 79], thought to be due to its well-known vasodilatory properties [63]. Anaemia was detected in about 50% of patients in a study by Penninga et al. but was mild and not clinically apparent in most [66]. Low-grade anaemia was shown to persist during a 2-year follow-up study, but not to progress.

Appropriate management of side effects may lead to successful long-term acceptance of medication. In several studies, the majority of side effects with anagrelide occurred within 1 month of starting therapy [65, 66, 68, 70, 71], with evidence showing that they subsided during continued treatment [65–71, 77, 80]. This effect is clearly

Table 2 Consensus definition of clinical resistance or intolerance to hydroxycarbamide in patients with essential thrombocythaemia (adapted from Barosi et al. [61])

Resistance/intolerance to hydroxycarbamide requires fulfilment of at least one of the following criteria:	
Platelet count of:	>600,000/μl after 3 months of treatment with at least 2 g/day hydroxycarbamide[a]
	>400,000/μl and leukocytes <2,500/μl at any dose of hydroxycarbamide
	>400,000/μl and haemoglobin <10 g/dl at any dose of hydroxycarbamide
Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxycarbamide	
Fever related to hydroxycarbamide	

[a] 2.5 g/day in patients with a body mass of >80 kg

illustrated in the study by Storen and Tefferi involving 35 patients younger than 50 years with ET [67]. Comparing initial (less than 3 months) and longer-term (over 3 months) anagrelide treatment, the incidence of headache was reduced from 34.2% to 5.7%, tachycardia from 22.8% to 8.5%, oedema from 14.2% to 5.7% and diarrhoea from 8.5% to 0% [67]. In contrast, a study by Birgegard et al. showed that the intensity of side effects remained the same in some patients with long-term treatment [63]. These findings suggest that it may be beneficial to inform patients of the possible reduction in side effects with time in order to improve compliance, especially in the early stages of treatment. Alternatively, it is feasible that this observed reduction was due to the withdrawal of patients who cannot tolerate anagrelide, hence only those patients experiencing milder side effects were recorded. However, in the study by Storen and Tefferi, no patients were lost to follow-up; therefore, it appears that the reduction in side effects might be related to improved tolerance to treatment with time.

For some ET patients, side effects can be prolonged and may lead to discontinuation of therapy: 0–50% of patients were withdrawn from anagrelide treatment in published studies [63, 64, 68, 69, 80], some because of lack of response and others because increasing the dose to an effective level was hindered by side effects.

Interferon-α

The interferon cytokine family demonstrates a wide range of biological properties, such as immune activation, as well as anti-proliferative and cell differentiation effects [81]. Based on these properties, interferon-α was first investigated for the treatment of ET in the late 1980s; however, it has never received an EU licence for a platelet reduction indication. The mechanism of action of interferon-α is thought to relate to its anti-proliferative effects on megakaryocytes, with reduction in platelet half-life also a contributing factor [82].

Interferon-α is effective in reducing platelet counts, with a mean overall response rate of 84.6% [59]. There has been no randomised comparison of interferon-α with other conventional therapies. Nevertheless, interferon-α is used off-label as a platelet-reducing alternative agent in MPDs, and is the only drug suitable for use during pregnancy [59]. It is of note that interferon-α is not known to be leukaemogenic [75].

Recent results in patients with PV indicate that interferon-α can reduce the percentage of cells expressing the *JAK2* mutant allele (i.e. the *JAK2V617F* allele burden) [83–85]. The biological and clinical significance of these results are unclear, and larger-scale studies are required to confirm the original findings. To date, no similar results have been published in patients with ET.

Common side effects of interferon-α include influenza-like symptoms, nausea, diarrhoea, myalgia, depression and fatigue [59, 86]. Side effects occur in nearly all patients at the start of treatment, but they generally abate [59]. For example, in the study by Yataganas et al. investigating the use of interferon-α in 18 patients with an MPD (nine with ET), influenza-like symptoms (e.g. fever higher than 38°C) lasted a maximum of 4–8 days following treatment initiation [87]. Despite this abatement, dropout rates between 15% and 66% have been reported, most commonly around 25% [88–90].

Given its immunomodulatory properties, interferon-α may result in symptomatic episodes of autoimmune disease such as hypothyroidism [91]. There have been reports of autoimmune thyroiditis [92], arthritis [93], hypertriglyceridaemia [94] and ischaemic optic neuropathy [95]. Mood disorders (depression/mania) are a well-documented side effect of interferon-α treatment [96–98], and limit the clinical utility of this agent in the treatment of ET.

The use of pegylated-interferon-α has also been investigated for the treatment of MPDs. This agent is formulated from interferon-α by attaching high molecular weight polymers of ethylene glycol [99]. Such chemical modification increases serum half-life and reduces renal excretion, thus allowing weekly, rather than daily, administration. Pegylated-interferon-α has been shown to effectively control platelet count and disease symptoms in patients with MPDs, including ET [88, 100–102]. However, in two studies of 38 and 42 patients with an MPD, pegylated-interferon-α had a similar tolerability profile to conventional interferon-α, with 26% and 50% of patients stopping therapy due to side effects and the level of toxicity limiting the duration of therapy [101, 102].

Risk stratification for treatment management

ET is a chronic condition with a prolonged clinical course that cannot currently be cured. Management, therefore, relies on the prevention of serious complications, specifically thrombohaemorrhagic events, through reduction of the platelet count or by altering platelet function. Management is stratified according to risk, categorised as high, intermediate and low, though the exact definition varies by investigator and country. In addition to traditional risk factors, which include previous thrombosis or major bleeding, age and elevated platelet count, other less traditional risk factors have also been suggested that may influence treatment decisions. They include cardiovascular risk factors and molecular markers (e.g. presence of PRV-1 or *JAK2* mutation) [103]. Whether the *JAKV2617F* mutation should be part of the risk stratification remains an area of uncertainty. Although evidence on whether the

JAK2V617F mutation increases the risk of thrombotic complications is conflicting [104–108], overall it appears that having the mutation is associated with a slightly higher risk. Some studies have indicated an association between leukocytosis and increased risk of thrombosis [10, 109, 110], and one study showed in a time-dependent analysis that the increased risk was corrected by hydroxycarbamide treatment [10]. It is possible that the leukocyte count is a prognostic marker for the activity of the MPD, but it remains to be proven by further study whether it is an important marker for treatment efficacy. The evidence for raised leukocyte levels being a risk factor for survival in ET is growing, but intervention studies are needed before white blood cell counts can be a basis for treatment decisions.

Taking into account the available evidence and clinical experience for various ET treatments, a suggested treatment algorithm is presented in Fig. 1. The following risk factors are suggested to define high-risk ET patients: (1) previous thrombosis or major bleeding; (2) age older than 60 years; or (3) very high platelet count (>1,500×10^9/l). Intermediate-risk ET patients are classified as those without high-risk criteria, but with hereditary thrombophilia or cardiovascular risk factors. Low-risk ET patients are without any of these risk factors.

For high-risk patients, hydroxycarbamide is standard therapy. However, due to the potential leukemogenicity of this drug, anagrelide or pegylated-interferon-α are possible alternative options in 'young' patients. This is a difficult issue and under much debate as currently no consensus has been reached upon evaluation of the available data. One has to bear in mind that ET patients have a near-normal life expectancy, which means that they may be subject to platelet-reducing therapy for many years. Prospective studies are needed to decide whether lowering of white blood cells is an important goal of treatment in ET, allowing risk/benefit decisions in the choice of treatment in younger patients. A watch-and-wait approach is recommended for low-risk patients, though low-dose aspirin may form part of the treatment strategy in this group. Aspirin should be avoided in patients with platelet counts exceeding 1,000×10^9/l and the combination of aspirin and anagrelide should be avoided in patients with previous major bleeding.

The platelet treatment goal is under debate. Previously, a standard goal was to lower platelet levels below 600×10^9/l. However, this threshold appears to be based on the previous diagnostic platelet level of >600×10^9/l, rather than evidence from clinical studies. Although there is only sporadic evidence that a lower treatment goal would provide better protection against thrombosis, since the new WHO diagnostic criteria use a platelet cut-off level of 450×10^9/l, in the current discussion a more stringent treatment goal of 400 or 450×10^9/l in ET patients has been suggested.

Special treatment problems

Patients may be partly unresponsive to any of the three common drugs for treating ET, or side effects may hinder a dose increase to an effective level. In these cases, combining two drugs may be an option. There are no studies exploring

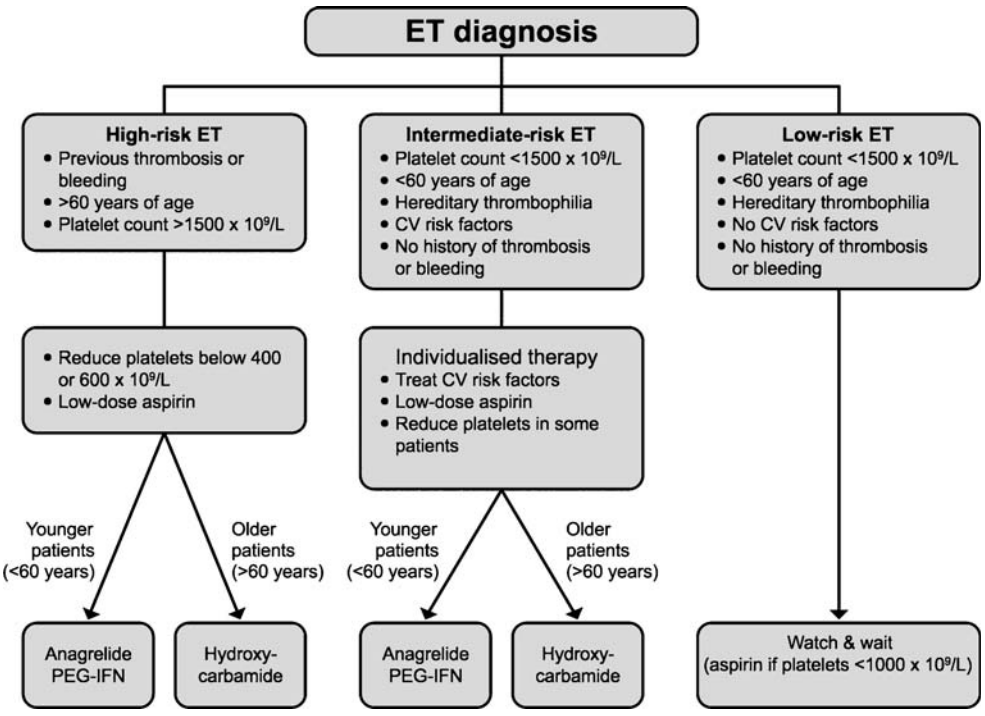

Fig. 1 Proposed treatment algorithm for patients with essential thrombocythaemia. Reproduced from Birgegard G. European Journal of Haematology 2007; 79 (Suppl. 68): 27–31 with permission of Blackwell Publishing. *CV*, cardiovascular; *ET*, essential thrombocythaemia; *IFN*, interferon-α. The age limit 60 years for the choice of first-line therapy is the personal opinion of the author

such combinations, nor is any combination therapy licensed for the treatment of ET, but in clinical practice it appears to be of good use. For example, a patient who develops anaemia or leukopenia from hydroxycarbamide may also benefit from receiving low-dose anagrelide, thus allowing the dose of hydroxycarbamide to be reduced and haemoglobin levels to be restored. Likewise, a combination of drugs may be beneficial for patients who cannot tolerate a dose increase of anagrelide or interferon-α to an effective level.

Patients intolerant to hydroxycarbamide, who either have cardiac insufficiency or are very old, constitute a special treatment problem. Anagrelide is not suitable in these patients, and neither is interferon-α. In this situation, busulphan may be an option, in spite of its leukaemogenic properties. A course of busulphan may provide sustained remission over many months, and the likelihood of developing leukaemia before death from other causes is low. On the same grounds, radioactive phosphorous is also an option.

During pregnancy it is not unusual for platelet levels to fall, but if platelet-reducing therapy is needed, interferon-α is the only recommended drug [111].

Possible future therapy developments

MPDs are clonal diseases and the ultimate goal must be to find a cure. However, the treatment of MPDs is a developing field. The detection of the *JAK2V617F* mutation may offer the opportunity for drug development and also provide a molecular marker for treatment efficacy. In PV, the reduction in *JAK2* allele burden with interferon-α treatment is of considerable interest [112], and similar findings have recently been found during hydroxycarbamide therapy in PV (personal communication). However, there have been no reports as to whether this is also true for ET. It is most likely that the *JAK2V617F* mutation is not the only molecular event responsible for development of PV and, therefore, although *JAK2* inhibitors are of great interest, they are unlikely to provide a cure. This is especially relevant in ET, where only half of patients carry the mutation, almost exclusively in heterozygous form [3]. However, if *JAK2* inhibitors prove to be effective for reducing platelet numbers, the discussion will concern whether the expected high cost of such drugs is warranted for symptomatic treatment. One can, therefore, expect the current platelet-reducing agents to maintain their place in the therapy of ET for the foreseeable future.

Conclusions

The objective of ET treatment is to reduce the risk of thromboembolic and haemorrhagic complications associated with the disorder. Treatment is given according to risk stratification: platelet reduction should be given in high-risk patients and selected intermediate-risk patients, whereas no treatment or aspirin should be used in low-risk patients. Hydroxycarbamide is currently first-line therapy in patients older than 60 years of age, whereas non-mutagenic drugs like anagrelide and interferon-α might be considered in younger patients and those clinically intolerant or resistant to hydroxycarbamide.

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